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## **NANOG Metabolically Reprograms Tumor-Initiating Stem-like Cells through Tumorigenic Changes in Oxidative Phosphorylation and Fatty Acid Metabolism.**

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### **Public Summary:**

Chia-Lin Chen, a CIRM predoctoral fellow, published outstanding papers in high impact journals with her mentor Keigo Machida, including Cell Metabolism and Gastroenterology as a first author. These papers focused on a cutting-edge cancer stem cell area including how a stemness gene, Nanog, metabolically reprograms cancer stem cells via tumorigenic changes in oxidative phosphorylation and fatty acid metabolism.

### **Scientific Abstract:**

Stem cell markers, including NANOG, have been implicated in various cancers; however, the functional contribution of NANOG to cancer pathogenesis has remained unclear. Here, we show that NANOG is induced by Toll-like receptor 4 (TLR4) signaling via phosphorylation of EzF1 and that downregulation of Nanog slows down hepatocellular carcinoma (HCC) progression induced by alcohol western diet and hepatitis C virus protein in mice. NANOG ChIP-seq analyses reveal that NANOG regulates the expression of genes involved in mitochondrial metabolic pathways required to maintain tumor-initiating stem-like cells (TICs). NANOG represses mitochondrial oxidative phosphorylation (OXPHOS) genes, as well as ROS generation, and activates fatty acid oxidation (FAO) to support TIC self-renewal and drug resistance. Restoration of OXPHOS activity and inhibition of FAO renders TICs susceptible to a standard care chemotherapy drug for HCC, sorafenib. This study provides insights into the mechanisms of NANOG-mediated generation of TICs, tumorigenesis, and chemoresistance through reprogramming of mitochondrial metabolism.

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